Immunogenicity and safety of the tick-borne encephalitis vaccination (2009-2019): A systematic review

Rampa, John Ethan ; Askling, Helena Hervius ; Lang, Phung ; Zens, Kyra Denise ; Gültekin, Nejla ; Stanga, Zeno ; Schlagenhauf, Patricia

Abstract: BACKGROUND Tick-borne encephalitis (TBE) is increasing in Europe. We aimed to evaluate the immunogenicity and safety of TBE-vaccination. METHODS This systematic review was registered at PROSPERO (CRD42020155737) and conducted in accordance with PRISMA guidelines. We searched CINAHL, Cochrane, Embase, PubMed, and Scopus using specific terms. Original articles, case reports and research abstracts in English, French, German and Italian were included for screening and extracting (JER; PS). RESULTS Of a total of 2464 records, 49 original research publications were evaluated for immunogenicity and safety. TBE-vaccines showed adequate immunogenicity, good safety and interchangeability in adults and children with some differences in long-term protection (Seropositivity in 90.6-100% after primary vaccination; 84.9%-99.4% at 5 year follow up). Primary conventional vaccination schedule (days 0, 28, and 300) demonstrated the best immunogenic results (99-100% of seropositivity). Mixed brand primary vaccination presented adequate safety and immunogenicity with some exceptions. After booster follow-ups, accelerated conventional and rapid vaccination schedules were shown to be comparable in terms of immunogenicity and safety. First booster vaccinations five years after primary vaccination were protective in adults aged <50 years, leading to protective antibody levels from at least 5 years up to 10 years after booster vaccination. In older vaccinees, > 50 years, lower protective antibody titers were found. Allergic individuals showed an adequate response and immunosuppressed individuals a diminished response to TBE-vaccination. CONCLUSIONS The TBE-vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed). TBE-vaccines are immunogenic in terms of antibody response but less so when vaccination is started after the age of 50 years. Age at priming is a key factor in the duration of protection.

DOI: https://doi.org/10.1016/j.tmaid.2020.101876

Rampa, John Ethan; Askling, Helena Hervius; Lang, Phung; Zens, Kyra Denise; Gültekin, Nejla; Stanga, Zeno; Schlagenhauf, Patricia (2020). Immunogenicity and safety of the tick-borne encephalitis vaccination (2009-2019): A systematic review. Travel Medicine and Infectious Disease, 37:101876.
DOI: https://doi.org/10.1016/j.tmaid.2020.101876

Travel Medicine and Infectious Disease 37 (2020) 101876

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Review

Immunogenicity and safety of the tick-borne encephalitis vaccination (2009–2019): A systematic review

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ARTICLE INFO

Keywords:
Booster
FSME
Immunogenicity
Priming
Safety
Surveillance
TBE
Vaccine
Vaccine failure

ABSTRACT

Background: Tick-borne encephalitis (TBE) is increasing in Europe. We aimed to evaluate the immunogenicity and safety of TBE-vaccination.

Methods: This systematic review was registered at PROSPERO (#CRD42020155737) and conducted in accordance with PRISMA guidelines. We searched CINAHL, Cochrane, Embase, PubMed, and Scopus using specific terms. Original articles, case reports and research abstracts in English, French, German and Italian were included for screening and extracting (JER; PS).

Results: Of a total of 2464 records, 49 original research publications were evaluated for immunogenicity and safety. TBE-vaccines showed adequate immunogenicity, good safety and interchangeability in adults and children with some differences in long-term protection (Seropositivity in 90.6–100% after primary vaccination; 84.9%–99.4% at 5 year follow up). Primary conventional vaccination schedule (days 0, 28, and 300) demonstrated the best immunogenic results (99–100% of seropositivity). Mixed brand primary vaccination presented adequate safety and immunogenicity with some exceptions. After booster follow-ups, accelerated conventional and rapid vaccination schedules were shown to be comparable in terms of immunogenicity and safety. First booster vaccinations five years after primary vaccination were protective in adults aged <50 years, leading to protective antibody levels from at least 5 years up to 10 years after booster vaccination. In older vaccinees, > 50 years, lower protective antibody titers were found. Allergic individuals showed an adequate response and immunosuppressed individuals a diminished response to TBE-vaccination.

Conclusions: The TBE-vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed). TBE-vaccines are immunogenic in terms of antibody response but less so when vaccination is started after the age of 50 years. Age at priming is a key factor in the duration of protection.

1. Introduction

Being endemic in 27 European countries with around 5′000–10′000 notified cases annually, tick-borne encephalitis (TBE) is one of the most important causes of viral encephalitis and the most frequent cause of viral meningitis in Europe [1–3]. TBE is geographically focused in Central and Eastern Europe, the Baltic States, the Russian Federation, and Japan, trending towards both an expansion of risk areas and an increase in incidence [2–7]. In Switzerland, incidence of TBE has increased significantly in the last few years, with more than 350 cases recorded in 2018 [8].

TBE is caused by the human pathogenic TBE virus, which is a member of the *Flaviviridae* family [3,4,9,10]. Three subtypes based on geographic origin and antigenic characteristics are of human importance: Far-Eastern, Siberian, and European [4,11]. Most European TBE cases are tick-transmitted by the ticks *Ixodes ricinus* with more than 100 species of wild and domestic animals acting as hosts reservoir [9,12,13]. Additionally, in certain areas TBE cases are transmitted from ingesting

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https://doi.org/10.1016/j.tmaid.2020.101876
Received 19 June 2020; Received in revised form 1 September 2020; Accepted 2 September 2020
Available online 12 September 2020

Box 1
Laboratory tests to measure anti-TBE-antibodies

Laboratory tests
NT – Neutralization Test [26,27] Serum sample or dilution of antibodies is mixed with a viral suspen- sion on top of host cells. Reaction of antibodies lead to antibody- mediated neutralization of the virus and protection of the host cells. Dilution of the sera leads to a minimum-protective concentration: a titer $\geq$ 1:10 is assumed to be protective.
ELISA – Enzyme-Linked Immunosorbent Assay [77,78] Serum sample or dilution of antibodies is mixed onto an assay with antibody binding sites. If binding takes place an enzyme mediated reaction takes place which can be recorded. An approach to standard- ise the results is to present them in Vienna international units/ml (VIEU/ml), whereas 1000 VIEU/ml were assigned to a standard serum.

unpasteurized milk or milk products of infected animals the so-called "alimentary TBE" and by *Dermacentor reticulatus* ricks respectively [10,14].

The disease TBE is reported more frequent in males [15]. In children the disease is milder [16]. Adults typically show a biphasic course: during the approximately one week long viremic phase, influenza-like symptoms (fever, fatigue, myalgia, and headache) occur [2,9,17]. Thereafter, most infected cases recover but around 5–15% develop a broad spectrum of neurological symptoms (ranging from mild meningitis to severe meningoencephalomyelitis) [8,9,17]. Long-term neurological sequelae are described frequently and 0.5–2% of all TBE cases were reported to be fatal [2,9,18–20].

No antiviral treatment against TBE exists [3,21,22]. Active vaccination is a practical preventive measure to reduce case numbers [10,21–23]. There are two inactivated virus vaccines licensed in Europe: FSME-Immun® (Pfizer), in some countries distributed as Ticovac®, and Encepur® (Bavarian Nordic) [24]. FSME-Immun® is based on the TBE virus strain Neudoerfl (Nd), whereas Encepur® is based on the TBE virus strain Karlsruhe-23 (K23) [18]. Both vaccines have a pediatric TBE vaccine variant [18].

To describe a vaccine's potential to prevent an infection, the two terms efficacy and effectiveness are used. While efficacy describes the effect measured in clinical trials (i.e. under ideal circumstances), effectiveness represents the results based on an epidemiological investigation under real world circumstances [25]. For the European TBE vaccines an effectiveness of 95–99% has been calculated in Austrian field studies [2,24]. To measure the immunogenicity specific TBE antibodies are evaluated using different laboratory test methods as listed in Box 1. The neutralization test (NT) is the most reliable to compare the TBE--vaccines' immunogenicity [26,27]. These antibodies show an age dependency with decreasing levels in elderly while keeping the same avidity. This immune aging process is termed immunosenescence [3,9].

2. Aim

Using a systematic review, we aimed to evaluate safety and immunogenicity of TBE-vaccination.

3. Methods

We systematically reviewed original research papers addressing European TBE-vaccines' immunogenicity and safety in accordance with PRISMA guidelines [28]. The systematic review was registered at PROSPERO: #CRD42020155737.

3.1. Study eligibility and search strategy

To identify appropriate studies, the following international databases were systematically searched with specific search terms as shown in Appendix 1: CINAHL, Cochrane, Embase, PubMed, and Scopus. Inclusion criteria were papers in English, French, German or Italian language, published in the period from January 1st, 2009, to August 31st, 2019, and being original articles, case reports or research abstracts. A Cochrane systematic review, published in 2009, summarizes important earlier findings, therefore, we decided not to include studies published earlier than 2009 [17]. Exclusion criteria were papers in other languages than the above mentioned and animal studies.

3.2. Data extraction

An evidence-table was created in Microsoft Word to extract the relevant data of original research (including population, intervention, control group, outcomes (PICO), study type, vaccines, laboratory analysis). To assess the methodological quality of the studies selected, we analyzed the strength of each study (original research and published abstracts) as displayed in Appendix 2.

3.3. Statistical analysis

Results of immunogenicity and safety for the TBE vaccines were investigated by two researchers (JER, PS) to conclude evidence-based recommendations in a narrative form. Different available laboratory

Table 1
Evidence-table of original research investigation on TBE vaccine immunogenicity.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Paulke-Korinek et al. [44] 2009 doi: 10.1016/j.vaccine.2009.09.068	booster cohort follow-up study	Booster vaccinations against tick-borne encephalitis: 6 Years follow-up indicates long-term protection Funding & sourcing: - Novartis Vaccines - Baxter	195 adults (at 6-year follow-up)	Encepur®	Neutralization Test titers ≥1:10	In 94% and 86% of TBE-vaccinated individuals aged below 60 and above 60 years, respectively, seropositivity was reported. Antibody levels are 2-fold lower in subjects above 60 years of age indicating a shorter period of protection against TBE.
Plentz et al. [51] 2009 doi: 10.1016/j.vaccine.2008.11.082	open label, multi center, booster cohort study	Long-term persistence of tick-borne encephalitis antibodies in adults 5 years after booster vaccination with Encepur® Adults Funding & sourcing: N/A	172 adults (at 5-year follow-up)	Encepur®	Neutralization Test titers ≥1:10	Seropositivity was found in 99% at 5-year follow-up after first booster dose (fourth dose) of Encepur® leads to protective antibody levels for up to 5 years.
Stiasny et al. [41] 2009 doi:10.1016/j.vaccine.2009.09.069	breakthrough infection analysis	Characteristics of antibody responses in tick-borne encephalitis vaccination breakthroughs Funding & sourcing: N/A	25 TBE-vaccine failures 25 control TBE patients	unspecified	ELISA Neutralization Test	Good antibody response will not necessarily prevent the disease in TBE vaccinated people. Discussing, that levels of neutralizing antibodies were too low in the vaccine breakthroughs, thus, supporting neutralizing antibodies to be the best surrogate for protection.
Jílková et al. [79] 2009 doi: 10.1517/14712590903066711	retrospective elderly cohort study	Serological response to tick-borne encephalitis (TBE) vaccination in the elderly - results from an observational study Funding & sourcing: - Baxter	185 adults (aged >60 years)	FSME-Immun® Encepur®	ELISA >126 VIEU/ml	Only 82% (n=152/185) of individuals receiving two dose TBE-vaccine showed seropositivity. Therefore 18% of vaccinees would have not been protected during the primary vaccination schedule. A difference of seropositivity rate reported in the two used vaccines: Individuals receiving FSME-Immun® presented seropositivity in 92% (n=97/105), whereas in individuals vaccinated with Encepur® seropositivity of 68% (n=54/80) was found.[3]
Loew-Baselli et al. [38] 2009 doi: 10.4161/hv.5.8.8571	open label, phase IV, multi-center, follow-up study	Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-Immun® 0.5 ml in adults aged 18-67 years Funding & sourcing: - Baxter	328 (at 3-year follow-up)	FSME-Immun® Encepur ®	Neutralization Test titers ≥1:10	Interchangeability of the two vaccines FSME-Immun® and Encepur® was demonstrated by vaccinating individuals with two doses of FSME-Immun® followed by either another dose of FSME-Immun® or Encepur®. This approach led to adequate antibody levels and adequate immune responses after following first booster vaccination with FSME-Immun® (seropositivity rate regardless of primary vaccination vaccines: 100%). 3-year seropositivity rate after three dose primary vaccination schedule 18-50 years old: 97.1% 51-67 years old: 87.3%
Wittermann, Petri et al. [50] 2009 doi: 10.1016/j.vaccine.2008.12.057	open-label, phase IV, multicenter, booster cohort study	Long-term persistence of tick-borne encephalitis antibodies in children 5 years after first booster vaccination with Encepur® Children Funding & sourcing: N/A	190 children (at 5-year follow-up) (aged 1-11 years)	Encepur Children®	Neutralization Test titers ≥1:10	Seropositivity at 5-year post booster in children was demonstrated to be 100% suggesting a booster interval up to 5 years in children vaccinated with Encepur® Children.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Wittermann, Schöndorf et al. [46] 2009 doi: 10.1016/j.vaccine.2008.10.003	**randomized, controlled, single blind study**	Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules Funding & sourcing: N/A	334 children (aged 1-10 years)	Encepur® Children FSME-Immun® Junior	Neutralization Test titers ≥1:10	A higher proportion of children achieved seropositivity following conventional primary vaccination schedule (3 dose Encepur®: 100%; 2 dose FSME-Immun® Junior and 1 dose Encepur®: 99%) compared to accelerated schedule (3 doses Encepur®: 100%; 2 doses FSME-Immun® Junior and 1 dose Encepur®: 96%). Results demonstrate that a primary vaccination course initiated with FSME-Immun® Junior can be completed with Encepur® Children and shows a high immunogenicity.
Andersson et al. [45] 2010 doi: 10.1016/j.vaccine.2010.02.001	retrospective data analysis of a Swedish cohort	Vaccine failures after active immunisation against tick-borne encephalitis Funding & sourcing: N/A	27 TBE-vaccine failures	FSME-Immun® Encepur®	ELISA (a 4-fold titer rise was regarded as significant for all the included assays)	Although vaccine failures were reported in all age groups, highest incidence of vaccine failures was in individuals aged above 50 years (70% n=19/27).
Pöllabauer, Fritsch et al. [47] 2010 doi: 10.1016/j.vaccine.2010.04.075	**randomized, double-blind, multi-centre dose finding study**	Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine Funding & sourcing: - Baxter	3697 children (aged 1-15 years)	FSME-Immun®[4]	ELISA >126 VIEU/ml	Investigation of 1640 children for immunogenicity demonstrated highest protective antibody response in groups with vaccine doses of 1.2µg after 3 dose primary vaccination schedule compared to doses of 0.3µg and 0.6µg. Results demonstrate high immunogenicity in individuals aged 1-15 years. Out of 763 children vaccinated with dose of 1.2µg (including 204 children aged 1-5 years and 208 children aged 6-15 years randomly assigned to that dose) seropositivity was reported to be 100%.[5]
Pöllabauer, Pavlova et al. [19] 2010 doi: 10.1016/j.vaccine.2010.04.047	**randomized, single blind, multi center, phase III comparison study**	Comparison of immunogenicity and safety between two paediatric TBE vaccines Funding & sourcing: N/A	303 children (aged 1-11 years)	FSME-Immun® Junior Encepur® Children	Neutralization Test titers ≥1:10	Reported data demonstrated high immunogenicity in both vaccines FSME-Immun® Junior and Encepur® Children. Seropositivity after two dose administration was 100% and 97.8% for FSME-Immun® Junior and Encepur® Children, respectively. FSME-Immun® in n (%) 1-2 years 50/50 (100%) 3-6 years 51/51 (100%) 7-11 years 49/49 (100%) total 1-11 years 129/129 (100%) Encepur® Children in n (%) 1-2 years 50/50 (100%) 3-6 years 49/51 (95.5%) 7-11 years 50/51 (97.5%) total 1-11 years 132/135(97.8)
Weinberger et al. [9] 2010 doi: 10.1016/j.vaccine.2010.03.024	prospective controlled study	Decreased antibody titers and booster responses in tick-borne encephalitis vaccinees aged 50–90 years Funding & sourcing: - Baxter	79 adults (aged 50-90 years)	FSME-Immun®	ELISA >155 VIEU/ml Neutralization Test titer ≥ 1:10	Antibody concentrations and NT titers were reported to be significantly lower in the older study population compared to younger populations. Close to equal low results were reported in the age group 50-59 compared to the age group >60 years. A booster vaccination around 5-7 years after last vaccine administration induced adequate antibody production even in the elderly.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Zlamy et al. [55] 2010 doi: 10.1016/j.vaccine.2010.10.002	controlled open-label follow-up study	Antibody dynamics after tick-borne encephalitis and measles-mumps-rubella-vaccination in children post early thymectomy Funding & sourcing: N/A	17 thymectomized individuals (aged 5-18 years) 20 controls[6]	FSME-Immun® Junior	ELISA	Four weeks after the third TBE vaccination thymectomized patients showed to have significant lower specific TBE-IgG antibody levels compared to healthy controls. At follow up of 220 weeks (4 years) specific IgG levels showed no significant difference. Data suggests that thymectomized patients possess a delayed but close to normal immune reaction. There was not found a gender related difference. Children infected with cytomegalovirus (CMV) did not show a difference in immune response compared to children not infected with CMV.
Orlinger et al. [4] 2011 doi:10.1093/infdis/jir122	cross-protectivity study	A tick-borne encephalitis virus vaccine based on the European prototype strain induces broadly reactive cross-neutralizing antibodies in humans Funding & sourcing: - Baxter BioSience	41 adults	FSME-Immun®	Neutralization Test	The study demonstrated in three-dose primary vaccinated individuals a cross-protectivity of FSME-Immun® against TBEV strains of the European, Far Eastern, and Siberian subtypes. Lower but still protective levels of neutralizing antibodies were found against the Omsk hemorrhagic fever virus.[7]
Askling et al. [37] 2012 doi: 10.1016/j.vaccine.2011.11.061	open-label, booster vaccine study	Immunogenicity of delayed TBE-vaccine booster Funding & sourcing: - Baxter - Center for Clinical Research in Sweden - Crucell - Novartis	260 adults	FSME-Immun®	Neutralization Test titers ≥5 ED_{50} (50% effective dose)	96% of the 260 individuals investigated showed adequate levels of neutralizing antibodies post-booster vaccination. No significant difference was found comparing normal or delayed booster intervals. Best booster response was found in individuals with prior ≥ 4 TBE-vaccine doses. Results demonstrate the interchangeability of FSME-Immun® and Encepur®, as the study population demonstrated adequate immune response after a booster dose of FSME-Immun® irrespective of prior vaccination history (FSME-Immun® or Encepur®). Authors support booster interval of at least 5 years after first booster dose (i.e. fourth dose).
Baldovin et al. [70] 2012 doi: 10.1002/jmv.23313	controlled immunogenicity cohort study	Persistence of immunity to tick-borne encephalitis after vaccination and natural infection Funding & sourcing: N/A	126 TBE vaccinees 66 naturally infected/immunized	FSME-Immun® TicoVac®	ELISA >126 VIE U/ml	Seropositivity was shown to be adequate in TBE vaccinees for up to 50 months after primary immunization and afterwards dropped rapidly to 50% at 70 months of follow-up. Three to eight Years after third dose, 79%-100% mean seropositivity was reported in subjects infected naturally (severity of the natural disease not mentioned). An age-related decline of seropositivity was described, starting three years after third dose of primary schedule. Individuals >60 years of age presented seropositivity in 66.7% compared to 91.7% in individuals <40 years of age. Authors recommend a booster interval of 3 years in age group >60 years and every 5 years in the age group <60 years. Except the first booster/fourth dose was suggested to be administered 3 years after third dose of primary schedule in all age groups.
Prymula et al. [18] 2012 doi: 10.4161/hv.20058	**randomized, single blind, multi center, phase III protectivity study**	Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® Children followed by third vaccination with FSME-IMMUN® Junior Funding & sourcing: - Baxter	296 children (aged 1-11 years)	FSME-Immun® Junior Encepur Children®	Neutralization Test titers ≥1:10	An adequate level of protective antibodies was found in children for the first tick season during primary vaccination schedule. Seropositivity of 95.3% and 91.0% was found after two doses of FSME-Immun® Junior and Encepur®, respectively. After third dose administration (FSME-Immun® Junior) a seropositivity of 100% was reported. Data concludes that two vaccinations with Encepur® Children can be successfully completed by a third dose of FSME-Immun® Junior.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Garner-Spitzer et al. [1] 2013 doi: 10.4049/jimmunol.1300293	age- and gender matched immunogenicity cohort study	Tick-borne encephalitis (TBE) and Hepatitis B nonresponders feature different immunologic mechanisms in response to TBE and influenza vaccination with involvement of regulatory T and B cells and IL-10 Funding & sourcing: N/A	67 adults	FSME-Immun®	Neutralization Test titers ≥1:10 for TBE Anti-HBs Ag levels >10mlU/ml for Hepatitis B	Authors demonstrated that Hepatitis B-vaccine non-responders were able to show an adequate immune response to the TBE-vaccine, therefore, suggesting non-responsiveness to be antigen specific.
Heinz et al. [34] 2013 doi: 10.3201/eid1901.120458	vaccination coverage and TBE incidence study	Vaccination and tick-borne encephalitis, central Europe Funding & sourcing: - Austrian Federal Ministry of health - Baxter - Czech Ministry of Health	TBE cases in Austria: 8493[8] Czeck Republik: 18196[8] Slovenia: 8129[8]	FSME-Immun® Encepur®	Serological tested individuals	A field effectiveness for regularly TBE-vaccinated individuals was estimated to be around 99% (best-case) and 96% (worst-case). In the regularly vaccinated aged 0-14 years, a field effectiveness of 92.2% to 94.0% (worst- and best-case scenario) was demonstrated. Field effectiveness (FE) being calculated with incidence of vaccinated (Iv) and non-vaccinated (In) individuals as followed [23]: $$FE\ (\%) = 100 \times (1 - \frac{Iv}{In})$$
Paulke-Korinek et al. [22] 2013 doi: 10.1016/j.vaccine.2012.12.075	booster follow-up study	Factors associated with seroimmunity against tick borne encephalitis virus 10 years after booster vaccination Funding & sourcing: - Novartis - Baxter	183 adults (at 10-year follow-up)	FSME-Immun®	Neutralization Test titers ≥1:10	Extrapolated cumulative seropositivity rate at 8- and 10-year post-booster follow-up of 86.8% and 77.3%, respectively, demonstrated long lasting protective immune memory in individuals vaccinated with FSME-Immun®. A significant difference in neutralizing antibody levels was found in individuals below and above 50 years of age. Age group 50-60 years and >60 years did not present a difference in protective antibody levels. Authors highlighting the need for booster interval recommendations to be adapted to age groups of younger and older than 50 years.
Beran et al. [40] 2014 doi: 10.1016/j.vaccine.2014.06.028	open-label, single centre, follow-up study	Five-year follow-up after a first booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates long-term antibody persistence and safety Funding & sourcing: - Novartis Vaccines	323 adults	Encepur®	Neutralization Test titers ≥1:10	In 313 adults with administered first booster dose following different primary vaccination schedules a seropositivity of 97-100% at five-year follow-up was reported.[9]
Lindblom et al. [80] 2014 doi: 10.1371/journal.pone.0100860	immunological cross selection study	Factors determining immunological response to vaccination against tick-borne encephalitis virus in older individuals Funding & sourcing: N/A	533 adults (median age of 61 (22-89) years)	FSME-Immun®	ELISA >126 VIE U/ml Neutralization Test titers ≥5	Data demonstrated that the most important factors determining the immunogenicity of the used vaccines are age and number of previous vaccine doses.[10] Seropositivity rate for # doses of (n) individuals 1 dose 52% of n=14 | 2 doses 33% of n=10 3 doses 59% of n=227 | 4 doses 84% of n=155 5 doses 96% of n=34

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Schosser et al. [36] 2014 doi: 10.1016/j.vaccine.2014.01.072	open-label, multi centre, booster catch-up study	Irregular tick-borne encephalitis vaccination schedules: The effect of a single catch-up vaccination with FSME-Immun®. A prospective non-interventional study Funding & sourcing: - Baxter	125 children (6-15 years) 1115 adults (≥16 years)	FSME-Immun® FSME-Immun® Junior	ELISA ≥25 U/ml	Data demonstrated that the most important factor for long time immunogenicity being the number of previous received vaccine doses regardless of time intervals between dose administration. Authors recommended an irregular or completed TBE vaccination series to be continued as if the previous vaccinations had been given according to a regular schedule ("every shot counts").[11] 1 previous vaccination: n(%): Children: 12/12 (100%); Young adults: 82/87 (94.3%); Elderly: 42/45 (93.3%) 2 previous vaccinations: n(%): Children: 79/80 (98.8%); Young adults: 229/231 (99.1%); Elderly: 111/115 (96.5%) 3 previous vaccinations: n(%): Children: 19/19 (100%); Young adults: 86/86 (100%); Elderly: 58/59 (98.3%) ≥4 previous vaccinations: n(%): Children: 14/14 (100%); Young adults: 299/300 (99.7%); Elderly: 187/192 (97.4%)
Schuler et al. [43] 2014 doi: 10.2807/1560-7917.ES2014.19.13.20756	Swiss surveillance Study	Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011 Funding & sourcing: N/A	65 TBE vaccinees	unspecified	Confirmation of the disease through IgM serum antibodies, IgG serum antibody seroconversion, a ≥4fold rise in IgG serum antibodies in paired serum specimens, or TBEV genome amplification	Out of 822 TBE cases with known immunization history, 65 individuals presented a history of at least one dose of TBE-vaccination. In 38 of them a complete three-dose primary vaccination history was documented, while 19 patients received the last dose less than three years and five patients more than five years before onset of the infection. Authors were not able to calculate if the rate of these TBE-vaccine breakthroughs were in limit of expected vaccine failures, as coverage of vaccinated people in Switzerland is not monitored.
Remoli et al. [81] 2015 doi: 10.1093/femspd/ftu002	controlled immunogenicity cohort study	Anti-tick-borne encephalitis (TBE) virus neutralizing antibodies dynamics in natural infections versus vaccination Funding & sourcing: N/A	101 TBE-vaccinees 62 naturally infected	FSME-Immun® Tico-Vac ®	ELISA and Neutralization test titers	In comparison to individuals which received completed three dose primary vaccination schedule, natural infected participants did not demonstrate an age-dependent decrease of neutralizing antibody levels.
Wittermann et al. [16] 2015 doi: 10.1016/j.vaccine.2015.02.038	open-label, phase IV follow-up extension study	Five year follow-up after primary vaccination against tick-borne encephalitis in children Funding & sourcing: - Novartis	267 children (aged 5-15 years)	Encepur® Children FSME-Immun® Junior	Neutralization Test titers ≥1:10	Results demonstrate high antibody levels following conventional (n=50) and accelerated (n=44) three-dose primary vaccination schedule with Encepur® Children for up to 5 years (seropositivity of 94-98%). Therefore, authors recommended first booster dose (fourth dose) in children vaccinated with Encepur® may be extended up to 5 years. Children receiving a mixed primary immunization series (2xFSME-Immun® + 1x Encepur® Children) did present a faster decrease of antibody levels with 65-70% showing seropositivity at three-year follow-up.
Aerssens et al. [57] 2016 doi: 10.1093/jtm/tav020	open-label, uncontrolled, booster cohort study	Analysis of delayed TBE-vaccine booster after primary vaccination Funding & sourcing: - Virion/Serion GmbH - Robert Koch Institute	88 adults (aged 25-54 years)	FSME-Immun®	Neutralization Test titers ≥1:10	Results demonstrated in 19 individuals (group 1) with primary vaccination history being 5-8 years ago, seropositivity in 53% and 94.7% at pre-booster and at post-booster investigation, respectively. In 69 patients (group 2) with primary vaccination history being ≥8 years (range: eight to 17 years) ago, 51% and 95.6% showed pre- and post-booster seropositivity. Authors conclude, that even 8 years after primary vaccination one booster dose of FSME-Immun® leads to protective antibody levels.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Beck et al. [48] 2016 doi: 10.1128/JVI.02985-15	comparison study of pediatric TBE-vaccine's immunogenicity	Molecular basis of the divergent immunogenicity of two pediatric tick-borne encephalitis virus vaccines Funding & sourcing: - Baxter - Pfizer Inc.	301 children (aged 1-11 years)	FSME-Immun® Junior Encepur® Children	Neutralization Test titers >1:7.7	Both, FSME-Immun® Junior and Encepur® Children presented adequate protective antibody levels towards the TBE virus strains K23 and Nd.[12] Age group / vaccine / (n) / K23 seropositivity in % / Nd virus seropositivity in % 1-2 / FSME-I. J.[34] / 50 / 100 / 100 1-2 / Ence. C.[34] / 50 / 100 / 94 3-6 / FSME-I. J.[34] / 51 / 100 / 100 3-6 / Ence. C.[34] / 51 / 100 / 96.1 7-11 / FSME-I. J.[34] / 48 / 100 / 100 7-11 / Ence. C.[34] / 51 / 100 / 96.1
Beškovnik et al. [52] 2016 doi: *N/A* *ISSN: 1581-0224* Journal: *Zdravniski Vestnik (2016) Vol. 85 (7-8); 375-382*	booster immunogenicity cohort study	Immunogenicity of a booster vaccination against tick-borne encephalitis Funding & sourcing: N/A	76 adults	booster: unspecified FSME-Immun® vaccination history	ELISA ≥10 U/ml	After a median interval of 15 years (8-16 years) seropositivity was found in 91.8% of 73 investigated adults and increased to 100% after booster vaccination.[13]
Hertzell et al. [54] 2016 doi: 10.1016/j.vaccine.2015.12.029	prospective, controlled, immunosuppressive immunogenicity study	Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: A prospective, open label multi-centre study Funding & sourcing: - Abbott - Novartis - Crucell - GlaxoSmithKline - Pfizer - Baxter	66 immunosuppressed patients[14] 56 controls	FSME-Immun® Encepur®	Neutralization Test titers of ED_{50} (50% effective dose) ≥5	Seropositivity of 39% (n=26/66) was reported in the immunosuppressed group, compared to 79% (n=44/56) in the healthy control group 13 months after three-dose primary vaccination schedule <60 years and four-dose primary vaccination >60 years. Authors conclude that immunosuppressed individuals must be carefully informed of their low-immunogenicity risk and should receive at least one extra dose of TBE-vaccination regardless of age.
Hopf et al. [35] 2016 doi: 10.1016/j.vaccine.2015.12.057	non-randomized, controlled, administration route study	Comparable immune responsiveness but increased reactogenicity after subcutaneous versus intramuscular administration of tick-borne encephalitis (TBE) vaccine Funding & sourcing: - Pfizer Vaccines	116 healthy adults	FSME-Immun®	Neutralization Test	Both intramuscular (n=58) and subcutaneous (n=58) TBE-vaccine administration presented adequate immune response in both genders for booster vaccination. No statement can be done about administration route efficacy in primary vaccination as participants have had a vaccination history.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Konior et al. [53] 2017 doi: 10.1016/j.vaccine.2017.03.059	prospective, follow-up cohort study	Seropersistence of TBE virus antibodies 10 years after first booster vaccination and response to a second booster vaccination with FSME-IMMUN 0.5 mL in adults Funding & sourcing: - Pfizer	315 adults (aged 21.70 years)	FSME-Immun®	Neutralization Test titers ≥1:10	Less than 80% of the individuals aged >60 years showed protective antibody titers prior to the fourth tick season. Therefore, authors confirmed a booster interval of 3 years for individuals above 60 years. An extension of booster vaccination intervals in people <50 years of age may be discussed as authors suggested. At ten-year follow up 262 individuals were investigated. Time after booster / Age group (years) / Seropositivity rate n (%) 3 years: overall (100%) 4 years: 18 – 49 n=239/245 (97.6%); 50 – 60 n=47/51 (92.2%); > 60 n=7/9 (77.8%) 5 years: 18 – 49 n=237/245 (96.7%); 50 – 60 n=47/51 (92.2%); > 60 n=6/8 (75.0%) 7 years: 18 – 49 n=227/245 (92.7%); 50 – 60 n=42/51 (82.4%); > 60 n=4/8 (50.0%) 10 years: 18 – 49 n=217/245 (88.6%); 50 – 60 n=38/51 (74.5%); > 60 n=3/8 (37.5%)
Lotrič-Furlan [42] 2017 doi: 10.1111/joim.12625	retrospective age and gender matched comparison study	Tick-borne encephalitis in patients vaccinated against this disease Funding & sourcing: - Slovenian Research Agency	39 TBE vaccine failures 78 TBE controls[15]	FSME-Immun®	Confirmation of the disease through IgG and IgM serum or intrathecal antibodies	TBE-vaccination failure was reported more often in older individuals and led to a more severe illness compared to age- and gender-matched controls developing TBE without previous vaccination history.
Dorko et al. [39] 2018 doi: 10.21101/cejph.a5271	immunogenicity cross sectional study	Effectiveness of primary vaccination against tick-borne encephalitis in employees of the armed forces Funding & sourcing: - VEGA grants[16]	101 adults (aged 22-49 years)	FSME-Immun®	Neutralization Test titers ≥1:10	FSME-I.J.[17] / Seropositivity: n (%) / median (range) time to last received vaccination 2 doses: 69.2% (n=9/13); 7 months (2-9 months) 3 doses: 90.9% (n=80/88); 8 months (0.5-34 months)
Garner-Spitzer et al. [56] 2018 doi: 10.1016/j.vaccine.2018.03.076	open-label, phase IV, controlled cohort study	Allergic patients with and without allergen-specific immunotherapy mount protective immune responses to tick-borne encephalitis vaccination in absence of enhanced side effects or propagation of their Th2 bias Funding & sourcing: - Pfizer - UCB Pharma - MSD - Baxter - Sanofi	49 allergic individuals 21 patients with specific immunotherapy 49 non-allergic controls	FSME-Immun®	Neutralization Test titers ≥1:10	Authors demonstrated sufficient TBE-antibody induced with TBE-booster vaccine in allergic individuals, even in them treated with specific immunotherapy.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Beran et al. [10] 2019 doi: 10.1016/j.vaccine.2017.12.081	open-label, phase IV, follow-up cohort study	Second five-year follow-up after a booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates at least 10 years antibody persistence Funding & sourcing: - GSK group companies - Novartis	206 individuals	Encepur®	Neutralization Test titers ≥1:10	In conventional, accelerated conventional, and rapid schedule adequate long-term protectivity up to ten years was demonstrated. **Seropositivity in all-screened set:** Time post-booster-dose / Group R (n=48) % (95% CI) / Group C (n=51) % (95% CI) / Group A (n=106) % (95% CI) 6 years: 96% (86 – 99); 100% (93 – 100); 97% (92 – 99) 7 years: 94% (83 – 99); 100% (93 – 100); 95% (89 – 98) 8 years: 90% (77 – 97); 98% (90 – 100); 93% (86 – 97) 9 years: 90% (77 – 97); 94% (84 – 99); 93% (86 – 97) 10 years: 90% (77 – 97); 94% (84 – 99); 93% (87 – 97) **Seropositivity in per-protocol set:** Time post-booster-dose / Group R (n) % (95% CI) / Group C (n) % (95% CI) / Group A (n) % (95% CI) 9 years: n=43; 100 (92 – 100); n=48; 100 (93 – 100); n=98; 100 (95 – 100) 10 years: n=43; 100 (92 – 100); n=49; 100 (89 – 100); n=99; 99 (96 – 100)
Hansson et al. [2] 2019 doi: 10.1093/cid/ciz176	retrospective data analysis of region Stockholm County	Tick-borne encephalitis vaccine failures: A 10-year retrospective study supporting the rationale for adding an extra priming dose in individuals starting at age 50 years Funding & sourcing: - Marianne and Marcus Wallenberg Foundation - Research Committee of Orebro lan - Hennes Kungliga H.[18]	53 vaccine failures 2 children (aged < 10 years)	unspecified	Confirmation of the disease through TBE specific IgM and IgG in sera or specific IgM in the cerebrospinal fluid, seroconversion in paired sera over time, or detection of TBE-RNA in a clinical specimen.	TBE breakthrough was mostly found in individuals aged >50 years. In age group ≥60 years with additional fourth priming dose (fourth dose) during primary vaccination no TBE-breakthrough occurred. Authors suggest an extra fourth priming vaccine dose starting from age 50. Further, a five-year booster-intervals was confirmed to be safe. Severity of the Disease: n=53 (100%) mild: n=10 (19%) moderate: n=21 (40%) severe: n=22 (42%) lethal: n=3 (6%) Days: median (range) in the ICU[19]: 21 (1-519) artificial ventilation: 21 (2-609)

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Inv.[2] Study Population	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Immunogenicity
Pöllabauer et al. [21] 2019 doi: 10.1016/j.vaccine.2019.03.032	prospective, open-label, phase IV, follow-up cohort study	Seropersistence and booster response following vaccination with FSME-Immun in children, adolescents, and young adults Funding & sourcing: - Pfizer	358 children (aged 1-15 years)	FSME-Immun® Junior	Neutralization Test titers ≥1:10	Seropositivity overall after three-dose primary immunization was 98.3%, 98.0%, 93.7%, and 84.9% at 2, 3, 4, and 5-year follow-up, respectively. Equal adequate immunogenicity was found in children below seven years of age compared to children in age groups 7-11 and 12-15 years. Further, results demonstrated a long-term seropositivity up to ten years in children after first booster dose (fourth dose) with FSEM-Immun® or FSME-Immun® Junior.

Five-year follow-up after **3rd dose**	Antibody seropositivity in % (n)	Five-year follow-up after **3rd dose**	Antibody seropositivity in % (n)
age group 1-2	84.9% (62/73)	age group 7-11	85.7% (114/133)
age group 3-6	95.6% (65/68)	age group 12-15	73.7% (56/76)
Follow-up after 4th dose	**Antibody seropositivity in % (n)**	**Follow-up after 4th dose**	**Antibody seropositivity in % (n)**
1 month	100.0% (171/171)	7 years	96.8% (151/156)
4 years	100.0% (147/147)	8 years	95.5% (149/156)
5 years	99.4% (155/156)	9 years	94.9% (148/156)
6 years	98.1% (154/157)	10 years	90.3% (140/155)

[1] Digital Object Identifier; [2] Inv. = Investigated; [3] Sixty vaccinees were excluded from analysis because rapid primary schedule was administered; [4] Dose-finding study of FSME-Immun® Junior; [5] For Immunogenicity analysis 1278 randomized (aged 1-15 years for dose finding study) and 362 non-randomized children (immune response after second dose) were investigated; [6] Age-matched and healthy controls; [7] FSME-Immun® itself consisting of TBE virus strain Neudoerfl; [8] In following years: Austria 1972-2011; Czech Republic 1973-2011; Slovenia 1970-2011; [9] Of the included 323 adults, ten were excluded because of death (n=4), loss of subjects at follow-up (n=2) and protocol deviations (n=4). Different Encepur® vaccination schedules used in this study were rapid (days 0, 7, 21), conventional (days 0, 28, 300), modified conventional (days 0, 21, 300), and accelerated conventional (0, 14, 300); [10] Two thirds of the investigated individuals were women (n=353); [11] Children aged <16 years; young adults aged 16-50 years (median 34 years); elderly aged ≥50 years (median 61 years); [12] FSME-I. J. = FSME-Immun® Junior; Ence. C. = Encepur® Children; [13] Three individuals were excluded for immunogenicity analysis because of possible cross-reactivity with other flavivirus antibodies; [14] 65 Rheumatoid Arthritis and one Morbus Bechterew patient; [15] Unvaccinated age- and gender-matched controls; [16] of the Ministery of Education, Science, Research and Sport of the Slovak Republic; [17] FSME-I.J. = FSME-Immun®; A statistically significant relationship was found between seropositivity and the number of vaccine doses. No statistical significance was identified in relation to age, sex and to time since administration of the last vaccine dose; [18] Hennes Kungliga H. = Hennes Kungliga Höghet Kronprinsessan Lovisas förening för barnasjukvard/Stifelsen Axel Tielmans Minnesfond; [19] ICU = Intensive Care Unit;

tests are used to quantify a vaccine's immunogenicity but this leads to difficulties in comparing study results. Therefore, in this systematic review a study's laboratory test methodology is labeled in Table 1 and Table 2. If available, the results acquired by an NT were used for interpretation.

4. Results

After removing duplicates and screening, 55 papers were selected for full-text assessment from the investigated databases. Three additional publications were identified for full-text assessment through checking the included papers' reference lists. Title-, abstract-, and full-text screening was conducted by two researchers (JER, PS). Of the 58 full-text assessed papers, 49 publications (40 pieces of original articles, five research abstracts of poster/oral sessions, three case reports and one case series) were investigated for immunogenicity and safety. Of the 40 original abstracts 26 showed external funding and/or sourcing, including 20 with connections to vaccine companies. Relevant data of published original articles were included into two comprehensive tables (Tables 1 and 2), while data from research abstracts and case reports/series were presented in a narrative form only. Nine studies were excluded for qualitative analysis after full-text assessment and were used for background information if relevant: Three systematic reviews were found and were considered for background discussion [13,17,29]. A further five reviews/expert opinions and one original article did not include relevant information for our analysis [3,11,30–33]. A PRISMA flow diagram (Fig. 1) demonstrates the selection process.

4.1. Immunogenicity (Table 1)

37 investigated original articles reported immunogenicity data. Fully vaccinated individuals regardless of the route of vaccination or delays in booster intervals were found to have an adequate immune response [10,18,21,34–40]. Data on primary vaccination schedules are displayed in Table 3. Furthermore, the European licensed vaccine FSME-Immun also showed cross protection against Far Eastern and Siberian TBEV strain subtypes [4]. In adults with allergies compared to vaccinees with no allergies, higher antibody levels were found after TBE-vaccination [22]. High levels of protective antibodies do not guarantee prevention of TBE [41]. Vaccine failure numbers were low and were associated with a more severe illness, occurring more often in elderly [2,42,43]. Detailed data on immunogenicity are shown in Table 1.

The elderly have lower antibody levels with a diminishing immune response starting in individuals aged >60 years and even in individuals aged ≥50 years [9,22,44]. Most investigated vaccine failures occurred in individuals aged ≥50 years but failures also occurred in younger individuals [2,45]. Further, individuals ≥60 years with an extra priming dose reported no TBE-vaccine failure [2].

In children, aged 1–15 years, the vaccine formulas of Encepur® and FSME-Immun® lead to high immunogenicity after primary vaccination of 95.6% up to 100% and high long-term seropositivity up to 5 years after primary vaccination [16,19,36,46–48]. There seems to be no age-related differences in the avidity and functional activity of antibodies induced by vaccination [2,49].

4.1.1. Booster-interval

In children, long term seropositivity for vaccine Encepur® Children and FSME-Immun® Junior were reported for up to 5 years, or 10 years, respectively after primary vaccination [38,50]. In adults both primary vaccination with Encepur® or FSME-Immun® lead to high long term seropositivity (77.3%–94% at ten year follow-up; 91.8% at a median of 15 year of follow-up) [10,22,44,51,52]. However, age groups >60 years showed a faster decline in seropositivity levels [38,44,53].

4.1.2. Interchangeability of TBE vaccines

For both adults and children TBE vaccines can be largely interchanged for primary and booster vaccination [18,37,38,46]. However, one study demonstrated a faster decrease in seropositivity in children receiving a mixed primary vaccination schedule (two doses of FSME-Immun® Junior followed by one dose Encepur® Children) [16].

4.1.3. Special groups

Seropositivity was found to be lower in 66 immunosuppressed patients compared to healthy individuals at 13 months follow-up after primary vaccination schedule [54]. In 17 thymectomized patients no significant differences in antibody levels compared to healthy controls was presented [55]. We found no papers on TBE vaccination in pregnant women. Allergic individuals with or without specific immunotherapy showed adequate immunogenicity [56]. Furthermore, Hepatitis-B vaccine failure showed no correlation to TBE-vaccine failure, as patients with Hepatitis-B vaccine failure were able to gain adequate TBE-vaccine immunogenicity [1]. We found no gender specific data on immunogenicity.

Table 2
Evidence-table of original research investigation on TBE vaccine safety.

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Safety
Loew-Baselli et al. [38] 2009 https://doi.org/10.4161/hv.5.8.8571	open label, phase IV, multi-center, follow-up study	Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-Immun® 0.5 ml in adults aged 18-67 years Funding & sourcing: - Baxter	FSME-Immun® Encepur ®	Neutralization Test titers ≥1:10	Safety assessed in 328 individuals FSME-Immun® booster reactions: SAE[2] n (%) 0/328 (0%) LR[2] n (%) 22/328 (6.7%) SR[2] n (%) 2/328 (0.6%) fever n (%) 0/328 (0%)
Wittermann, Schöndorf et al. [46] 2009 https://doi.org/10.1016/j.vaccine.2008.10.003	**randomized, controlled, single blind study**	Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules Funding & sourcing: N/A	Encepur® Children FSME-Immun® Junior	Neutralization Test titers ≥1:10	334 children assessed for safety Pain at the injection site (%) of all (n) 1st dose E.C.[3] ≤ 36% of 117 2nd dose E.C.[3] ≤ 26% of 116 1st dose F-I.J.[3] ≤ 31% of 120 2nd dose F-I.J.[3] ≤ 31% of 118 Fever > 39°C after 1st dose all vaccines 1.8% of 334 2nd dose all vaccines 0.9% of 331 Serious adverse events: 0% of 334
Pöllabauer, Fritsch et al. [47] 2010 https://doi.org/10.1016/j.vaccine.2010.04.075	**randomized, double-blind, multi-centre dose finding study**	Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine Funding & sourcing: - Baxter	FSME-Immun®[4]	ELISA >126 VIEU/ml	Safety analysis in 2417 children 1-5 years of age n (%) Restlessness 53/584 (9.1%) 6 – 15 years of age (n) fatigue 102/1833 (5.6%) Malaise 76/1833 (4.2%) 1 – 15 years of age n (%) Injection site pain 272/2417 (11.3%) Tenderness 438/2417 (18.1%) Nausea 76/2417 (3.1%) serious AE 0/2417 (0%) fever at 1stdose[5] 230/2374 (9.7%) Fever in age group n (%) 1-2 years 66/183 (36.1%) 3-6 years 72/559 (12.9%) 7-15 years 92/1540 (5.4%) total (1-15 years) 230/2374 (9.7%)
Pöllabauer, Pavlova et al. [19] 2010 https://doi.org/10.1016/j.vaccine.2010.04.047	**randomized, single blind, multi center, phase III comparison study**	Comparison of immunogenicity and safety between two paediatric TBE vaccines Funding & sourcing: N/A	FSME-Immun® Junior Encepur® Children	Neutralization Test titers ≥1:10	Safety assessed in 302 individuals[6] injection site reactions first vaccination FSME-IJ [6] 19/150 (12.7%) Ence. C. [6] 44/152 (28.9%) injection site reactions second vaccination FSME-IJ [6] 13/150 (8.7%) Ence. C. [6] 34/152 (22.4%) Fever after first | second vaccination FSME-IJ[6] 12/150 (8%) |2/149 (2.0%) Ence. C. [6] 14/152 (9.2%)|7/152 (4.6%) SAE[6] 0/203 (0%)
Schumacher et al. [59] 2010 https://doi.org/10.1016/j.vaccine.2010.04.002	retrospective data analysis of Swiss data bases[7]	Surveillance for adverse events following immunization (AEFI) in Switzerland–1991-2001 Funding & sourcing: - Federal Office of Public Health Switzerland	unspecified	N/A	73 reported TBE-vaccine adverse events between 1991 – 2001 were investigated.[8] Mild adverse events n=4/73 (5.5%) SAE n=19/73 (26%) Allergic reactions n=3/73 (4.1%) Local reactions n=0/73 (0%) Systemic reactions n=42/73 (57.5%)

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Table 2 (*continued*)

Author, Year doi:[1)]: (#)	Study Type	Original Study Title Funding & Sourcing	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Safety
Mad'ar et al. [82] 2011 https://doi.org/10.21101/cejph.a3634	retrospective data analysis of diabetic patients	Vaccination of patients with diabetes mellitus – a retrospective study Funding & sourcing: - Avenier Inc.	FSME-Immun® Encepur®	N/A	TBE-vaccination was performed using Encepur® (n=6) and FSME-Immun® (n=223) without increasing the risk of serious adverse events.
Askling et al. [37] 2012 https://doi.org/10.1016/j.vaccine.2011.11.061	open-label, booster vaccine study	Immunogenicity of delayed TBE-vaccine booster Funding & sourcing: - Baxter - Center for Clinical Research in Sweden -Crucell -Novartis	FSME-Immun®	Neutralization Test titers of ED_{50} (50% effective dose) ≥5	Total of 260 individuals assessed for safety. AE[9)] at injection site pain: n=22/260 tenderness: n=25/260 mild AE[9)]: n=25/260 (10%) SAE[9)] events: n=0/260 (0%)
Prymula et al. [18] 2012 https://doi.org/10.4161/hv.20058	**randomized, single blind, multi center, phase III protectivity study**	Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® Children followed by third vaccination with FSME-IMMUN® Junior Funding & sourcing: - Baxter	FSME-Immun® Junior Encepur Children®	Neutralization Test titers ≥1:10	298 children were assessed for adverse events[10)] systemic reactions: 1-2y: 1.0%; 3-6y: 4.0%; 7-11y: 11.1% local reactions: 1-2y: 3.0%; 3-6y: 4.0%; 7-11y: 0.0% Serious adverse events: 1-2y: 2.0%; 3-6y: 17.0%; 7-11y: 30.3%
Paulke-Korinek et al. [22] 2013 https://doi.org/10.1016/j.vaccine.2012.12.075	booster follow-up study	Factors associated with seroimmunity against tick borne encephalitis virus 10 years after booster vaccination Funding & sourcing: -Novartis -Baxter	FSME-Immun®	Neutralization Test titers ≥1:10	In adults suffering of allergies (including atopy and anaphylactic allergies) significant higher antibody levels were found compared to individuals without allergy.
Beran et al. [40] 2014 https://doi.org/10.1016/j.vaccine.2014.06.028	open-label, single centre, follow-up study	Five-year follow-up after a first booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates long-term antibody persistence and safety Funding & sourcing: - Novartis Vaccines	Encepur®	Neutralization Test titers ≥1:10	278 adults were analyzed for adverse events. pain 55% swelling 6% erythema 8% Systemic solicited reactions: 30% myalgia 17% malaise 7% headache 14% nausea 4% arthralgia 5% fever 1% SAE[11)] 5% SAE[11)]
Aerssens et al. [57] 2016 doi: 10.1093/jtm/tav020	open-label, uncontrolled, booster cohort study	Analysis of delayed TBE-vaccine booster after primary vaccination Funding & sourcing: - Virion/Serion GmbH - Robert Koch Institute	FSME-Immun®	Neutralization Test titers ≥1:10	Total of 88 individuals were analyzed for safety Total adverse events n=7/88 (8%) Mild adverse events n=2/88 (2.3%) Systemic reactions n=5/88 (5.7%) Fever and/or malaise n=2/88 (2.3%)
Hertzell et al. [54] 2016 https://doi.org/10.1016/j.vaccine.2015.12.029	prospective, controlled, immunosuppressive immunogenicity study	Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: A prospective, open label multi-centre study Funding & sourcing: - Abbott - Novartis - Crucell - GlaxoSmithKline - Pfizer - Baxter	FSME-Immun® Encepur®	Neutralization Test titers of ED_{50} (50% effective dose) ≥5	Safety investigation included 122 individuals. One immunosuppressed individual suffered of gastroenteritis two days after first dose vaccination. There were no Serious adverse drug reactions reported.
Hopf et al. [35] 2016 https://doi.org/10.1016/j.vaccine.2015.12.057	non-randomized, controlled, administration route study	Comparable immune responsiveness but increased reactogenicity after subcutaneous versus intramuscular administration of tick-borne encephalitis (TBE) vaccine Funding & sourcing: - Pfizer Vaccines	FSME-Immun®	Neutralization Test titers	116 adults were assessed for safety analysis[12)] **local reactogenicity (SC / IM)** n=54/58 (93.2%) / n=29/58 (50%) **local pain (SC / IM)** n=44/58 (75.9%) / n=26/58 (44.8%) **fever (SC / IM)** n=0/58 (0%) / n=2/58 (3.4%)

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Table 2 (*continued*)

Author, Year doi:[1]: (#)	Study Type	Original Study Title Funding & Sourcing	Vaccine(s)	Antibody methodology Measure of seropositivity	Outcome: Safety
					systemic reactions (SC / IM) n=20/58 (34.5%) / n=24/58 (41.4%) **SAE** n=0/116 (0%)
Oberle et al. [60] 2016 doi: 10.1097/INF. 0000000000001073	retrospective analysis of German pediatric database ESPED[13]	Anaphylaxis after immunization of children and adolescents in Germany Funding & sourcing: N/A	1 unspecified 1 strain K23 (probably Encepur®)	N/A	2 of 22 post-immunization anaphylactic incidences in Germany between June 01, 2008 and May 31, 2010 occurred after TBE-vaccination. Based on 3'125'546 administered doses of TBE vaccine in Germany, the incidence was calculated at 0.69 (0.67 – 1.2) [1.0 (0.99 – 1.4)] (Point Estimate and 95% confidence interval) per million TBE doses administered.[14]
Konior et al. [53] 2017 https://doi.org/10.1016/j. vaccine.2017.03.059	prospective, follow-up cohort study	Seropersistence of TBE virus antibodies 10 years after first booster vaccination and response to a second booster vaccination with FSME-IMMUN 0.5 mL in adults Funding & sourcing: - Pfizer	FSME-Immun®	Neutralization Test titers ≥1:10	47 individuals were assessed for Safety data mild adverse events: (fatigue, injection pain, malaise) n=2/32 (4.3%) Serious adverse events: n=0/47 (0%)
Garner-Spitzer et al. [56] 2018 https://doi.org/10.1016/j. vaccine.2018.03.076	open-label, phase IV, controlled cohort study	Allergic patients with and without allergen-specific immunotherapy mount protective immune responses to tick-borne encephalitis vaccination in absence of enhanced side effects or propagation of their Th2 bias Funding & sourcing: - Pfizer - UCB Pharma - MSD - Baxter - Sanofi	FSME-Immun®	Neutralization Test titers ≥1:10	119 individuals (70 allergic, 49 controls) were investigated for safety data. There was found no risk increase for exacerbations and for difference in adverse events rate of the allergic groups in comparison to the non-allergic group.[15] **local reactions:** **n (%)** allergic no SIT[15] group 23/49 (50%) males: 0/19 (0%) females: 23/30 (77%) allergic + SIT[15] group 12/21 (57.1%) males: 5/9 (56%) females: 7/12 (58%) control group 27/49 (55.1%) males: 6/19 (32%) females: 21/30 (70%) **systemic reactions:** **n (%)** allergic groups 31/70 (44.3%) control group 23/49 (46.9%)
Pöllabauer et al. [21] 2019 https://doi.org/10.1016/j. vaccine.2019.03.032	prospective, open-label, phase IV, follow-up cohort study	Seropersistence and booster response following vaccination with FSME-Immun in children, adolescents, and young adults Funding & sourcing: - Pfizer	FSME-Immun® Junior	Neutralization Test titers ≥1:10	In 231 children assessed for adverse events, no vaccine-related serious adverse events or deaths were reported.

[1] Digital Object Identifier; [2] SAE = Serious adverse events; LR = Local reactions; SR = Systemic reactions; Systemic reactions were considered not to be related to the vaccination; [3] E.C. = Encepur® Children; F–I.J. = FSME-Immun® Junior; [4] Dose-finding study of FSME-Immun® Junior; [5] Fever at 2nd dose only reported being much lower than 1st dose. Fever showed age dependency; [6] FSME-IJ = FSME-Immun® Junior; Ence. C. = Encepur® Children; SAE = Serious adverse events; Both vaccines present well tolerance in children 1–11 years of age. A significant lower rate of injection site reaction was reported after vaccination with FSME-Immun® Junior compared to Encepur® Children. Close to equal were both vaccines in terms of systemic reactions and fever. Fever was reported more often in children aged 1–2 years compared to other age groups and injection site reaction was showing the lowest rate in this age group; [7] based on all reports received by the Swiss Federal Office of Public Health or the National Drug Pharmacovigilance Center ("Schweizerische Arzneimittelne-benwirkungszentrale"); [8] In a passive reporting system, such as the ones investigated, milder events tend to be reported at a lower rate making numbers of SAE overrepresented. Incidence of serious adverse events reported to be 2.3 (95%CI: 1.4–3.5) per 100′000 distributed TBE-vaccine doses. Incidence of any adverse drug reactions for any kind of vaccine was described to be 2.7 per 100′000 distributed vaccine doses; [9] AE = adverse events; SAE = serious adverse events; [10] 298 children assessed for adverse events within seven days of third vaccination dose. No statistically significant differences between Encepur® Children and FSME-Immun® Junior for first and second vaccination reported; [11] SAE = serious adverse events; SAE were considered unrelated to the study vaccine by the authors and happened during the long follow-up time. Elective surgeries were not considered as SAE. During the study period four deaths occurred (two grade IV glioblastomas, one myocardial infarction and one suicide). As the suicide did not receive intervention it was not included into the safety analysis, therefore, only three deaths are included into SAE; [12] SC = subcutaneous; IM = Intramuscularly; SAE = serious adverse events; There was a significant lower local adverse event rate of redness, swelling and local pain in the intramuscularly route compared to the subcutaneous; [13] ESPED – Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (German pediatric surveillance unit); [14] Half the anaphylaxis cases following unspecific vaccinations occurred after the first dose. Authors conclude that either another component in the vaccine was the origin of the anaphylaxis or another molecular pathway without need of sensitization started the anaphylaxis; [15]SIT = specific immunotherapy; In the group with specific immunotherapy females showed an equal frequency on adverse events compared to males, whereas females in the group without specific immunotherapy and in the healthy control group showed higher adverse events rate than men in the same groups.

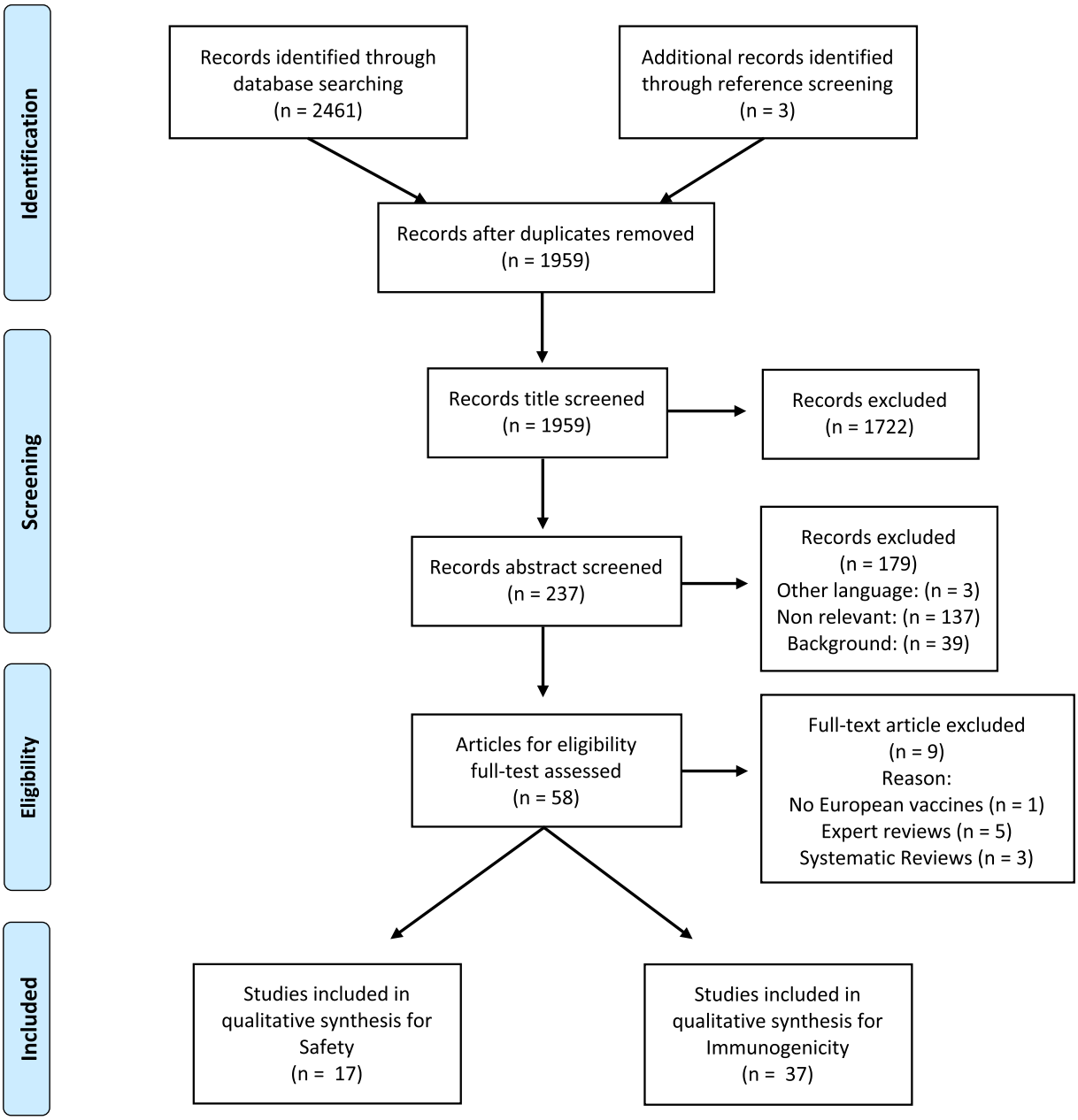

Fig. 1. Prisma flow diagram.

4.2. Safety (Table 2)

17 original articles reported safety data. Local reactions/mild adverse events such as pain at the injection site, tenderness or local swelling were described in 24.8% (4.3–54%) of study participants [18,19,35,37,38,40,46,53,56,57]. Systemic reactions were reported in about 30% (0.6–45.9%) of vaccinees [18,35,38,40,56]. Fever was reported in 3.4% (0–9.7%) of vaccinees [18,19,35,38,40,46,47]. Systemic reactions were reported to be lower after the 2nd dose compared to the first dose administration [19]. Higher rates of local and systemic reactions were reported in 7–11 year old children compared to 1–2 and 3–6 year old age groups [18]. In adults, no age pattern of adverse events was found. Furthermore, the application route led to differences in adverse event reporting: A significantly lower local adverse event rate of redness, swelling and local pain in the intramuscular administration group compared to the subcutaneous group was reported. Systemic reactions were reported to be increased in the intramuscular group, however, this was not statistically significant [35].

Ten studies in our analysis comprising 4455 vaccinees reported no serious adverse events (SAE) [18,19,21,35,37,38,46,47,53,54]. Three studies described SAE: One Encepur® booster five-year follow-up study reported an incidence rate of 5% in 278 adults. These SAE were considered by the authors to be “life events” during the long follow-up and not related to the vaccination (including two grade IV glioblastomas and one myocardial infarction), the possibility of an etiologic link was suggested by Strojnik in 2017 describing neurotropic viral genome in glioblastoma cells [40,58]. The second study reporting SAE was a surveillance study in a passive Swiss reporting system and it described 19 SAE after unspecified TBE-vaccine administration, leading to a calculation of an incidence rate of 2.3 SAE in 100′000 distributed doses of vaccine [59]. The third publication, a retrospective analysis of a German pediatric surveillance database, presented two cases of anaphylactic shocks after TBE vaccination (one unspecified vaccine, one based on K23 – probably Encepur®). Based on TBE vaccines

Table 3
Primary vaccination schedules and immunogenicity.

Author	Seropositivity[b]
Years after TD[a]	
Loew-Baselli et al. [38]	
3 years after TD with F&E[c]	
Age group 18-50	97.1%
Age group 51-67	87.3%
Prymula et al. [18]	
28 days after TD[a] with	
2x Ence. C.[d] + 1x FSME-I. J.®[e]	100%
3x FSME-Immun® Junior	100%
Beran et al. [40]	
5 years after TD[a] with Encepur®	
Conventional schedule[f]	100%
Rapid schedule[f]	100%
Accelerated schedule[f]	99%
Aerssens et al. [57]	
≥8 years after TD[a] with FSME-I. J.®[e] J	
age range 8–17 years[g]	51%
Dorko et al. [39]	
8 months[h] after TD[a] with FSME-I. J.®[e]	90.9%
Pöllabauer et al. [21]	
4 years after TD[a] with FSME-I. J.®[e]	
total (age 1–15 years)	93.7%
5 years after TD[a] with FSME-I. J.®[e]	
total (age 1–15 years)	84.9%
age group 1-2	84.9%
age group 3-6	95.6%
age group 7-11	85.7%
age group 12-15	73.7%

[a] TD = third dose.
[b] Seropositivity = NT titers ≥ 1:10.
[c] F&E = FSME-Immun® and Encepur®.
[d] Ence C. = Encepur® Children.
[e] FSME I.J. = FSME-Immun® Junior.
[f] Demonstrated in per-protocol set, whereas in all-screened set at five-year follow-up: conventional schedule = 94%, rapid schedule = 90%, accelerated schedule = 93%.
[g] Demonstrated in 69 patients.
[h] Median with a range of 0.5–34 months.

administration numbers in Germany, the incidence was calculated at 0.69 (0.67–1.2) [1.0 (0.99–1.4)] (Point Estimate and 95% confidence interval) per million TBE-doses administered [60].

Based on the data it wasn't possible to identify sex patterns of adverse events. Although one paper showed adverse events to be reported at a higher rate in healthy females and in allergic females without specific immunotherapy compared to healthy men and allergic men without specific immunotherapy [56]. Further data about safety is displayed in Table 2.

4.3. Research abstracts and case reports/series

4.3.1. Immunogenicity and safety data

Four research abstracts of poster-/oral sessions and one case series reported data on immunogenicity in thymectomized children (presented in 2009) or juvenile idiopathic arthritis (JIA) patients (presented in 2015) [61,62]. An adequate response was achieved in these groups after full vaccination. In a cohort study of 33 adults a lower antibody response was found in individuals aged 60–80 years compared to age group 21–31 years (presented in 2012) [63]. Another controlled cohort study demonstrated an adequate protective antibody level after primary TBE vaccination in elderly [64]. One case-series described four reported vaccine failures: one patient was deemed not to be a vaccine failure case (no second booster vaccination), two individuals to be probable vaccine failures and one case to be a confirmed vaccine failure [24].

Three case reports and one case series reported safety data. Jiménez et al. described the use of a statistical measure, the Information Compound (IC) measure of association. An IC score of 3.0 was found for TBE vaccines suggesting a statistical association between TBE vaccine and facial paralysis, compared to an IC score of 3.1 for a H1N1 influenza pandemic vaccine, an IC score of 3.0 for a hepatitis b/a vaccine or an IC score of 2.3 for a yellow fever vaccine [65]. Another case report described the reactivation of immune thrombocytopenic purpura by a TBE vaccination (FSME-Immun®) with subsequent recovery [66]. A 3-case series investigated excessive daytime sleepiness and narcolepsy-cataplexy starting a few weeks, one month, and two months after TBE vaccination (vaccine unspecified) [67]. In an expert opinion forum, a case of a 2 year old-child with facial paralysis presenting two days after second TBE dose was considered to be unrelated to the TBE-vaccination [68].

Table 4
Summary of vaccination recommendations in different countries.

Recommendations	Switzerland [83]	Germany [72]	Austria [74]	Sweden [73]
Age recommendations for start of vaccination	6 years[a]	no specific age[b]	1 year (6 months: 3 + 1 schedule)	Depending on risk of exposure
Primary schedule in months	3 doses	3 doses	3 doses	3 doses <50 years 4 doses >50 years
FSME-Immun®	0, 1, 6	0, 1–3, 5–12 after 2nd	0, 1–3, 5–12 after 2nd	0, 1–3, 5–12 after 2nd
Encepur®	0, 1, 10	0, 1–3, 9–12 after 2nd	0, 1–3, 9–12 after 2nd	0, 1–3, 5–12 after 2nd
>50 years				0, 1, 3 after 2nd, 5–12 after third dose
Accelerated/Rapid schedules				
FSME-Immun®	0, 14 days, 5–12 months[c]	0, 14 days, 5–12 months	0, 14 days, 5–12 months	N/A[d]
Encepur®	0, 7, 21 days[c]	0, 7, 21 days	0, 7, 21 days	N/A[d]
First booster interval				
primary schedule[e]	10 years	3 years	3 years	3 years
Rapid schedule[e]	N/A	12–18 months	12–18 months	N/A
2nd and following Booster intervals:				
<50 years	10 years	5 years	5 years	5 years
50–59 years	10 years	3 years	5 years	5 years
≥60 years	10 years	3 years	3 years	5 years

[a] Below six years individual risk-benefit estimation.
[b] Individuals below 3 years of age should be taken into consideration.
[c] Swiss government vaccine advice documents only described rapid schedules as being available. Exact timing was taken according to the manufacturer's package insert.
[d] Rapid schedule described as available but not to prefer if possible.
[e] After regular primary schedule or after primary rapid schedule with the vaccine Encepur® used.

5. Discussion

Our systematic review found TBE vaccines Encepur® and FSME-Immun® to be highly immunogenic, well tolerated and in all studies except one to be interchangeable. There were some conflicting results with regard to age at first vaccination and booster intervals and the timing of vaccine administration and the use of accelerated schedules (Table 3). The immunogenicity of these vaccines has been shown to be adequate after primary vaccination and following booster doses in all age groups. The duration of seropositivity in individuals aged ≥50 years was reduced and studies point to reduced long-term protection in older

Table 5
Main findings from the systematic review.

Elderly >60 years
Immunosenescence [9,22,44,70]
Diminishing immune system starting at 50–60 years
Booster Interval [53,70]
Adequate immunogenicity up to three years after a TBE vaccine dose
Recommendation: Booster doses (≥4 doses) every three years for >60 years
Children 1–15 years [19,38,46,47]
Well tolerated and safe vaccination with Encepur® Children andFSME-Immun® Junior
First Booster dose timing <50 years
Encepur® & FSME-Immun® [21,40]
Adequate protectivity five years after last dose of primary vaccination
Recommendation: First booster dose five years after primary vaccination
Subsequent Booster intervals <50 years
Encepur® & FSME-Immun® [10,52,53]
Adequate protectivity ten years after first booster (fourth dose) vaccination
Recommendation: Subsequent booster intervals every ten year
Booster intervals 50–60 years
Encepur® & FSME-Immun® [9,53]
Lower immune response and faster decrease of protective antibody levels
Recommendation: Early transition from ten- to two-year booster intervals
Interchangeability of Encepur® and FSME-Immun®
Interchangeable [18,37,38,46]
Adequate Immunogenicity after mixed vaccine administration
Diminished protectivity [16]
Faster decrease of protective antibodies following mixed primaryvaccination schedule
Recommendation: Use of mixed vaccination only in exception and with administration of earlier subsequent booster vaccination.

adults. In terms of safety, the European, licensed vaccines were found to be well tolerated in both children (aged 1–17 years) and in adults, with local injection site reactions in 24.8% (4.3–54%) and systematic reactions in 30% (0.6–45.9%) of vaccinees. Vaccine related serious adverse events (SAE) were rare.

The conventional TBE vaccination schedule (0,28, 300 days) was superior to other schedules in the short-term only [31,46]. Studies show that long-term immunogenicity, after several booster vaccinations, was comparable regardless of the primary vaccination schedule [29,40]. Nevertheless, rapid vaccination schedules should be administered only in individuals requiring protection within a short timespan (such as travellers).

The interchangeability of the two European vaccines was shown in several publications except one from Wittermann et al. which showed a faster decline of antibody levels after a mixed primary vaccination schedule [16,18,37,38,46]. It appears that a mixed vaccine approach can be considered but is not optimal.

Many countries consider that the primary vaccination schedule protects for at least 3 years (Austria, Germany, Sweden), whereas in Switzerland the recommended first booster dose is ten years after the primary schedule [69]. The evidence from this systematic review supports an earlier first booster dose at 3–5 years in children and adults [16,21,51,52,70].

Subsequent booster intervals of at least 5 years in healthy adults were recommended in five studies and indeed, adequate post-booster protection from 5 years up to ten years for adults and/or children was confirmed [2,10,21,37,40,50]. Our results show a safe immunogenicity of TBE-vaccines for up to ten years after booster vaccination in healthy children (seropositivity at ten year follow-up: 90.3%) and adults below 60 years (seropositivity at ten year follow-up: 77.3%–94%) although lower immunogenicity was observed in adults > 50 years of age. Older individuals who have had a 4-dose primary schedule show longer duration of seropositivity after booster doses [2]. Therefore, to ensure protection of older people, recommendations should include a fourth vaccination during the primary schedule and shorter booster intervals [2,22,54].

Evidence on immunogenicity and safety of TBE vaccination in special risk groups remains scant. In a cohort of 70 allergic individuals an immune response after TBE-vaccination was comparable to healthy controls [56]. In studies with limited numbers, immunosuppressed patients showed a lower immune response compared to healthy individuals [54,71]. For thymectomized individuals the evidence shows only an early decreased immune response later approaching levels comparable to healthy controls [55,61]. Immunosuppressed groups must be informed of their high-risk status and should receive an extra dose of TBE-vaccine for primary vaccination regardless of age. There are research gaps: We found no studies documenting incidental TBE vaccine use in pregnant or breastfeeding women. There are few data on use of the vaccine in diabetic patients. Study results were rarely stratified by age and sex, although there are some indications that this is important.

TBE vaccines have both shown to be well tolerated in children and adults with a lower rate of injection site reactions reported with FSME-Immun® Junior compared to Encepur® Children [17–19]. In 10 out of 13 investigated studies analyzing SAE in 4455 individuals no SAE were recorded [18,19,21,35,37,38,46,47,53,54]. In a 5-year follow up study, an incidence rate of 5% SAE was reported for 313 investigated individuals. These SAE were considered “life events” unrelated to the vaccine [40]. In a Swiss surveillance study of 73 adverse events in the years 1991–2001 following TBE-vaccination 19 presented to be SAE corresponding to a rate of 2.3 SAE per 100,000 distributed doses. This time span includes the application of the old mouse-brain derived TBE vaccines [59]. Another study of a German pediatric surveillance database described anaphylactic shock after TBE-vaccination and showed an SAE incidence of 0.69 (0.67–1.2) [1.0 (0.99–1.4)] per million TBE doses administered [60]. In summary, SAE associated with TBE vaccination are rare.

The issue of the timing and the frequency of booster doses is important: Swiss vaccine recommendations, issued by the Federal Office of Public Health, recommend administration of TBE-vaccine to all healthy individuals (>6 years old) in all areas except the cantons of Geneva and Ticino. The primary vaccination schedule should be administered, depending on the vaccine used, at months 0, 1 and 5–12. Thereafter booster vaccinations are recommended every 10 years in all age groups [8]. Swiss recommendations for booster vaccines differ from other countries’ guidelines where boosters are recommended at earlier intervals [72–74] (Table 4).

Vaccination coverage of TBE vaccination is not actively monitored in Switzerland and therefore it is not possible to describe actual coverage, amount of used vaccines or field effectiveness of TBE-vaccines in the Swiss population. An unpublished report suggests a national TBE vaccination coverage of 9.5% for four TBE doses (personal communication Vasiliki B). In Austria Heinz et al. described a field effectiveness for regularly TBE-vaccinated individuals estimated to be around 99% under best case scenario and 96% under worst-case assumptions [34]. To increase coverage, Switzerland’s rules for vaccination availability were adapted in 2015: certain cantons allowed community pharmacists with vaccination certification to administer specific vaccines, such as TBE-vaccine without prescription [75]. To expand coverage of TBE-vaccine, the Swiss army recommended voluntary TBE-vaccinations in young recruits, since 2007 [76]. Because service is only mandatory for Swiss men, there needs to be found another way to reach Swiss females and those who are not of Swiss nationality.

A strength of this Systematic Review is that it was conducted in accordance with PRISMA guidelines [28]. Five online databases were searched to include all the important publications and to summarize most important evidence for the European TBE-vaccines and the main results are highlighted in Table 5. Limitations of this systematic review were the different approaches of the included and investigated studies making outcomes hard to compare. Per example different laboratory tests used like Enzyme-linked Immunosorbent Assay (ELISA) and NT may not always be comparable. With regard to capturing SAE, most of the vaccine studies investigated, had a small sample size and were not powered to detect rare or SAE. Surveillance systems did identify SAE

reports. Many of the key studies were conducted directly or funded by TBE vaccine manufacturers. Future surveillance systems need to be strengthened to enable detection of very rare adverse events as well as TBE cases to allow finetuning of risk assessment. Additionally, more research must be done on sex differences in TBE vaccine response and booster intervals for individuals 50–59 years of age, impact of age at priming and on vaccine response in the immunocompromised. To further evaluate TBE vaccine recommendations, it is essential to continuously follow up all previously vaccinated TBE cases with respect to the number of doses and the time of vaccination. This information should be collated in a vaccination register to avoid memory or reporting biases.

In conclusion, TBE vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed) and be age adjusted. TBE vaccines are immunogenic in terms of antibody response but less so when vaccination is started later than the age of 50 years. Age at priming is a key factor in the duration of protection.

Conflicts of interest

None of the authors have relevant conflicts of interest to declare.

Acknowledgements

This study was funded, in part, by the Federal Office of Public Health, Switzerland and by the Competence Centre, MilMedBiol, a research collaboration between the University of Zürich and the Swiss Armed Forces

Appendix

Appendix 1
Detailed search strategy and keywords in the five databases CINAHL, Cochrane, Embase, PubMed, and Scopus

Search Step	CINAHL	Cochrane	Embase	PubMed	Scopus[1)]
1	tick borne disease	tick-borne encephalitis	'tick borne encephalitis'/exp	Encephalitis, Tick-Borne[2)]	tick AND borne AND encephalitis
2	encephalitis, tick borne	Publication Year > 2009	'tick borne encephalitis'	Encephalitis[3)]	tick-borne AND encephalitis
3	tick-borne encephalitis	Date added to database <August 31, 2019	'tick-borne' AND 'encephalitis'	tick-borne[3)]	fsme
4	encephalitis, tick-borne	1 AND 2 AND 3	'fsme'	tick-borne encephalitis[3)]	1 OR 2 OR 3
5	fsme		Combine 1–4 with OR	tick borne encephalitis[3)]	adjuvant
6	Combine 1–4 with OR		'adjuvant'	Fsme[3)]	adverse AND reactions
7	adjuvant		'adverse' AND ('reactions' OR 'events')	Combine 1–6 with OR	side AND effects
8	adverse (reactions AND events)		'side' AND 'effects'	Viral Vaccines[2)]	adverse AND events
9	side AND effects		'pediatric'	Drug-Related Side Effects and Adverse Reaction[2)]	gender AND effects
10	gender AND effects		'child' OR 'children'	Adjuvant[3)]	gender
11	pediatric		'elderly'	adverse AND (reactions OR events)[3)]	Pediatric OR Child OR children
12	child OR children		'immunosenescence'	side AND effects[3)]	Elderly
13	Elderly		'gender'	side AND effect[3)]	immunocompromised
14	immunosenescence		'sex'	gender AND effect[3)]	sex
15	gender OR sex		'immunocompromised'	Pediatric[3)]	viral AND vaccines
16	immunocompromised		'viral' AND ('vaccines' OR 'vaccination')	child or children[3)]	viral AND vaccination
17	viral AND (vaccines OR vaccination)		'virus' AND ('vaccines' OR 'vaccination')	immunocompromised[3)]	virus AND vaccines
18	virus AND (vaccines OR vaccination)		'protect' OR 'protection'	Elderly[3)]	virus AND vaccination
19	safety AND (vaccines OR vaccination)		'dosage' OR 'dose'	immunosenescence[3)]	immunosenescence
20	protect OR protection		Combine 6–19 with OR	gender OR sex[3)]	vaccines AND safety
21	dosage OR dose		Publication Year 2009–20,19[4)]	protect OR protection[3)]	protect OR protection
22	Combine 7–21 with OR		Date added to database between January 01, 2009 and 31/08/20,19[6)]	viral AND (vaccines OR vaccination)[3)]	vaccination AND safety
23	Publication time between January 2009 and August 2019		5 AND 20 AND 21 AND 22	virus AND (vaccines and vaccination)[3)]	dosage OR dose
24	6 AND 22 AND 23			safety AND (vaccine OR vaccination)[3)]	Combine 5–23 with OR
25				dosage OR dose[3)]	Publication Year 2009–20,19[7)]
26				Combine 8–25 with OR	4 AND 24 AND 25
27				Publication Date[5)] January 01, 2009–August 31, 2019	
28				7 AND 26 AND 27	

[1)] Search-type for Scopus: Title-Abs-Key (…);[2)] Search type: " …" [Mesh];[3)] Search type " …" [All Fields];[4)] Original search: (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py);[5)] ("2009/01/01"[PDAT]: "2019/08/31"[PDAT]);[6)] [1-1-2009]/sd NOT

[1–9]/sd;[7]) (LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2019) OR LIMIT-TO(PUBYEAR, 2018) OR LIMIT-TO(PUBYEAR, 2017) OR LIMIT-TO(PUBYEAR, 2016) OR LIMIT-TO(PUBYEAR, 2015) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009).

Appendix 2

Strength of original research assessment table

Author, Year	Randomized	Concealed allocation	Controlled	Blinding	Inclusion of >90% patients in analysis	Dropouts described	comments
Jílková [79] 2009	NO	–	YES	open-label	NO (75.5% included in final analysis)	Adequate	1/3 of study population in rapid schedule excluded
Loew-Baselli [38] 2009	NO	–	YES	open-label	Immun: NO (60.7% at 3yfu[1)])	appropriate only from follow-up time point	
Paulke-Korinek [44] 2009	NO	–	NO	open-label	Immun: YES	Adequate	
Plentz [51] 2009	NO	–	NO	open-label	Immun: YES	Adequate	
Stiasny [41] 2009	NO	–	YES	N/A	YES	No dropouts	retrospective analysis of vaccine failures
Wittermann [20] 2009	YES	–	YES	single-blind	Immun.: YES Safety: YES	No dropouts	
Wittermann [50] 2009	NO	–	NO	open-label	NO (81.9% at 5yfu[1)])	Adequate	
Andersson [45] 2010	NO	–	NO	–	YES	No dropouts	retrospective analysis of vaccine failures
Pöllabauer [47] 2010	Immune assessment: YES Safety assessment: NO	N/A	IMMUN: YES SAFETY: NO	IMMUN: double-blind SAFETY: open-label	IMMUN: YES SAFETY: YES	Numbers provided – reasons not described	
Pöllabauer [19] 2010	YES	N/A	YES	single-blind	YES	Yes	
Schumacher [59] 2010	NO	–	NO	–	YES	N/A	retrospective safety data analysis
Weinberger [9] 2010	NO	–	YES	N/A	YES	NO	
Zlamy [55] 2010	NO	–	YES	open-label	N/A	N/A	
Mad'ar [82] 2011	NO	–	NO	open-label	YES	N/A	retrospective data analysis
Orlinger [4] 2011	NO	–	NO	–	YES	N/A	
Askling [37] 2012	NO	–	NO	open-label	NO (83% included)	YES	313 included, 53 lost to follow-up
Baldovin [70] 2012	NO	–	YES	N/A	YES	No dropouts	
Prymula [18] 2012	YES	YES	YES	single-blind	YES	NO	
Garner-Spitzer [1] 2013	NO	–	YES	N/A	YES	N/A	
Heinz [34] 2013	–	–	–	–	YES	N/A	vaccination coverage and TBE incidence study
Paulke-Korinek [22] 2013	NO	–	NO	open-label	NO (42.6% at 10yfu[1)])	appropriate	follow up study
Beran [40] 2014	NO	–	YES	NO	Immun: YES Safety: NO (78% included)	appropriate	Follow-up Study
Lindblom [80] 2014	NO	–	NO	N/A	YES	No dropouts	
Remoli [81] 2014	No	–	YES	open-label	YES	N/A	
Schosser [36] 2014	NO	–	NO	open-label	NO (42.6% included)	appropriate	2915 enrolled subjects and 1240 (42.6%) included for analysis
Schuler [43] 2014	NO	–	NO	open-label	N/A	N/A	Surveillance study
Wittermann [16] 2015	NO	–	YES	open-label	After 3 years group of 111 discontinued	appropriate	follow-up study
Aerssens [57] 2016	NO	–	NO	open-label	YES	No dropouts	
Beck [48] 2016	YES	Unknown	YES	Unknown	YES	No Dropouts	All tested sera included into analysis
Beškovnik [52] 2016	NO	–	NO	N/A	YES	appropriate	
Hertzell	NO	–	YES	open-label	YES	No Dropouts	

(continued on next page)

Appendix 2 (*continued*)

Author, Year	Randomized	Concealed allocation	Controlled	Blinding	Inclusion of >90% patients in analysis	Dropouts described	comments
[54] 2016 Hopf	YES	N/A	YES	N/A	YES	No Dropouts	
[35] 2016 Oberle	NO	–	NO	–	N/A	N/A	surveillance study
[60] 2016 Konior	NO	–	NO	open-label	YES	appropriate	
[53] 2017 Lotrič-Furlan	NO	–	YES	open-label	YES	No Dropouts	TBE-breakthrough data analysis (no intervention)
[42] 2017 Dorko	NO	–	NO	open-label	YES	No Dropouts	observational study/no intervention
[39] 2018 Garner-Spitzer	No	–	YES	open-label	YES	No Dropouts	
[56] 2018 Beran	NO	–	YES	open-label	NO (51.5% at 10yfu[1)])	appropriate	
[10] 2019 Hansson	NO	–	NO	open-label	YES	No dropouts	retrospective database analysis
[2] 2019 Pöllabauer	NO	–	NO	open-label	NO (87% at 10yfu[1)])	appropriate	179 enrolled into 10yfu from 205 receiving 2nd booster dose (87%) and 358 from earlier study
[21] 2019							

[1)] yfu = years of follow-up.

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